

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208313Orig1s000

OTHER ACTION LETTERS



NDA 208313

COMPLETE RESPONSE

Sun Pharmaceutical Industries Limited
Attention: Karin A. Kook, Ph.D.
U.S. Agent for Sun Pharmaceutical Industries Limited
Salamandra, LLC
One Bethesda Center
4800 Hampden Lane, Suite 900
Bethesda, Maryland 20814-2998

Dear Dr. Kook:

Please refer to your New Drug Application (NDA) dated March 29, 2015, received March 30, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for INFUGEM (gemcitabine injection), 10 mg/mL.

We acknowledge receipt of your amendment dated November 23, 2016, which constituted a complete response to our November 24, 2015, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

1. During recent inspections of the Sun Pharmaceutical Industries Limited, FEI: 3002809586, manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

In addition, we have the following comments and recommendations:

PRESCRIBING INFORMATION

2. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

3. Provide justification that the dose banding instructions in Section 2 of the prescribing information, which would result in an inherent approximation of the recommended dose, do not affect the safety and efficacy of the drug in its conditions of uses.

CARTON AND CONTAINER LABELING

4. Submit draft carton and container labeling revised as follows:
 - a. Please remove (b) (4).
 - b. Delete (b) (4) "in 0.9% sodium chloride" in the established name.
 - c. Revise (b) (4) to "Each 100 mL contains: gemcitabine 1,000 mg, equivalent to gemcitabine HCl USP 1,138 mg".
 - d. Revise storage condition to be consistent with PI as "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [see USP Controlled Room Temperature]. Do not freeze."

PROPRIETARY NAME

5. Please refer to correspondence dated, February 14, 2017, which addresses the proposed proprietary name, INFUGEM. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

6. Describe in detail any significant changes or findings in the safety profile.
7. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
8. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 9. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 10. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
 11. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 12. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 13. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings

Between the FDA and Sponsors or Applicants of PDUFA Products,” March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Ms. Missiratch (Mimi) Biable, Senior Regulatory Health Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Joseph Gootenberg, M.D.
Deputy Director
Division of Oncology Products 2
Office of Hematology and Oncology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH E GOOTENBERG
05/23/2017



NDA 208313

COMPLETE RESPONSE

Sun Pharmaceutical Industries Limited
Attention: Karin A. Kook, Ph.D.
U.S. Agent for Sun Pharmaceutical Industries Limited
Salamandra, LLC
One Bethesda Center
4800 Hampden Lane, Suite 900
Bethesda, Maryland 20814-2998

Dear Dr. Kook:

Please refer to your New Drug Application (NDA) dated March 29, 2015, received March 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Gemcitabine Hydrochloride Injection, 10 mg/mL.

We acknowledge receipt of your amendments dated June 4, 11, and 26; July 2, 13, and 28; August 18 and 25; and September 22 and 29, 2015.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

1. During a recent inspection of the Sun Pharmaceutical Industries Ltd manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

MANUFACTURING PROCESS

- 2.



HUMAN FACTOR STUDY

We recommend the following comments be implemented prior to commencing the gemcitabine hydrochloride in sodium chloride injection summative human factors study.

3. Review the protocol for inconsistencies. For example, error debrief is listed in the test script, but not in the testing procedure description.
4. Clarify who the intended end user is for the proposed IFU. If the IFU is meant for nurses and pharmacists, then it is unclear why body surface area (BSA) and Target Dose are provided in the IFU. Revise the IFU to remove this information, or provide rationale for including the BSA and Target Dose in the IFU.
5. It appears the proposed product is intended for patients with BSAs ranging from 1.2 m² to 2.6 m²; however, the IFU contains the statement (b) (4)
Clarify whether the proposed product is intended for use with patients with BSAs ranging from 1.2 m² to 2.6 m², or if it is only intended for use with the specific BSAs listed in the IFU table (e.g. 1.2 m², 1.3 m², 1.4 m², etc.).
 - a. If it's intended for the range of BSAs from 1.2 m² to 2.6 m², then provide prescribing instructions on dose banding and clarification on how dose banding should be performed for BSA values with two decimal places. For example, if a patient has a BSA of 1.75 m² and requires a dose of 1,000 mg/m² (calculated dose is 1,750 mg), then is the correct dose after dose banding 1700 mg, or 1800 mg?
 - b. If it's intended for the specific BSAs listed in the IFU table, then evaluate the effectiveness of the statement "For the treatment..." under step 1 of IFU in the human factors study to provide assurance that nurses and pharmacists will not use the proposed product for a patient with BSA of 1.75 m².
6. To better simulate a real life scenario in the identification and differentiation of tasks, the IFU may be provided to the human factor study participants, but do not instruct the participant to review the IFU prior to receiving their prescription card in the human factor study. In the usual clinical setting, the end user (pharmacist or nurse) would receive the prescription first. If the end user needs help with interpretation or calculation of dose, he or she would have the option to refer to the PI and/or IFU that are packaged with the drug.
7. Nurses will be required to administer two bags in some cases. We recommend inclusion of tasks that would assess how effective the product labeling and the IFU are in addressing the risk of omission of the second bag to be infused by the nurse.

PRESCRIBING INFORMATION

8. As currently proposed, the prescriber would not be aware that the pharmacist or nurse could potentially round the prescribed dose to available bag strength. This rounding of dose without notifying the prescriber could possibly be regarded as prescribing by the nurse or pharmacist. Thus, your currently proposed labeling plan could be error prone. You should consider incorporating a table in the Dosage and Administration section of the Prescribing Information that instructs the prescriber to round the dose.
9. Assigning National Drug Codes (NDC) (b) (4)
(b) (4)
(b) (4) To better differentiate National Drug Codes, thus differentiate the different strengths, we recommend changing the product codes (b) (4)
10. We reserve additional comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

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When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

11. Describe in detail any significant changes or findings in the safety profile.
12. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
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13. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
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You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Ms. Missiratch (Mimi) Biable, Senior Regulatory Health Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Joseph Gootenberg, M.D.
Deputy Director
Division of Oncology Products 2
Office of Hematology and Oncology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH E GOOTENBERG
11/24/2015